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CV

Stine Hangaard Casper finished her Bachelor´s degree in Occupational Therapy at the University College of Northern Denmark in 2010. Subsequently, Stine completed her Master of Science degree in Clinical Science and Technology in 2012 at Aalborg University. During her studies, Stine worked as an occupational therapist within the psychiatric field and as a research assistant within the field of telehealth and heart disease. After her studies, Stine worked as a research assistant at a telehealth project at Aalborg University before she began employment as a coordinator at a health center in the North Denmark Region.

In January 2014, Stine enrolled as a PhD student in the Doctoral School at the Faculty of Medicine, Aalborg University, under the supervision of Professor Ole Hejlesen. Concurrently with her PhD related research, Stine has worked on the European project "eWALL" solving various research-related tasks. During the course of her PhD, Stine has been on maternity leave twice.

ENGLISH SUMMARY

Chronic obstructive pulmonary disease (COPD) is a chronic lung disease characterized by airflow limitation. All patients with relevant respiratory symptoms who have been exposed to known risk factors for COPD should be considered for diagnostic evaluation. A diagnosis of COPD is based on spirometry. A post-bronchodilator forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) <0.7 confirms the presence of COPD. It is essential that COPD be diagnosed correctly so that appropriate treatment can be initiated. However, COPD remains highly underdiagnosed and misdiagnosed. Spirometry, although problematic, is the key pulmonary function test in COPD diagnosis and monitoring. The problems related to spirometry underline the need for alternative approaches to COPD pulmonary function testing.

The overall aim of this thesis was twofold. First, the thesis aimed to explore the challenges of underdiagnosis and misdiagnosis of COPD. Second, the thesis aimed to explore alternatives to existing methods of COPD pulmonary function testing. The thesis is based on four studies represented in Papers I-IV. Papers I-II addressed the first aim of the thesis, whereas Paper III-IV addressed the second aim of the thesis.

Paper I explored characteristics of patients with undiagnosed COPD. Subjects from the National Health and Nutrition Examination Survey (NHANES) (2007-2012) with spirometry-based obstruction (n=1098) were included. The subjects were divided into two groups: undiagnosed and diagnosed. Various statistical tests were performed to compare 51 factors characterizing the two groups. The study found that subjects without a COPD diagnosis were characterized by better respiratory health and overall health than subjects diagnosed with COPD.

Paper II explored causes of misdiagnosis of COPD through a scoping review. The search of literature was performed in PubMed, EMBASE, and CINAHL. After a thorough review process, 73 papers were included in the final sample. The 73 papers were synthesized into five themes describing causes of misdiagnosis of COPD. This study found that COPD misdiagnosis was mainly caused by factors related to spirometry.

Paper III aimed to improve the spirometry-based diagnosis of COPD by adjusting the pre-bronchodilator threshold. Subjects from NHANES (2007-2012) who had undergone post-bronchodilator spirometry (n=680) were included. The pre-bronchodilator threshold was varied while the accuracy, sensitivity, specificity,

negative predictive value, and positive predictive value were calculated. The results showed that an adjustment of the threshold from 0.70 to 0.66 improved classification rates potentially minimizing misclassification of COPD.

Paper IV aimed to validate the Simple Pulmonary Oxygen Transfer Test (SPOT test) – a novel pulmonary function test for COPD. Subjects with COPD visiting the respiratory medicine clinic at Aalborg University Hospital (n=14) were included. The subjects underwent pulmonary function testing including the SPOT test and the test of diffusion capacity of the lungs for carbon monoxide (DLCO). Pearson's product moment correlation was used to calculate the correlation between the SPOT test and DLCO. The study found a significant correlation between the SPOT test and DLCO underlining the potential of the SPOT test as a future pulmonary function test in COPD.

In conclusion, the diagnosis of COPD proves problematic. Patients with undiagnosed COPD seems to be characterized by better respiratory health than diagnosed patients. Thus, the comprehensive underdiagnosis of COPD may, in part, be explained by the fact that respiratory symptoms are mild in the early stages of COPD. The causes of misdiagnosis of COPD are many, and they are mainly linked to the key pulmonary function test, spirometry. Spirometry is associated with a multitude of biases; in particular, the spirometry threshold is much discussed and is a major cause of misdiagnosis. An adjustment of the pre-bronchodilator threshold from 0.7 to 0.66 may improve COPD diagnosis by limiting misclassification. However, such an adjustment is inadequate, and there is a need for alternative pulmonary function tests for COPD. The SPOT test shows promise as a new pulmonary function test in COPD. However, further studies are needed to ensure the validity and the future role of the SPOT test in COPD diagnosis and monitoring.

DANSK RESUME

Kronisk obstruktiv lungesygdom (KOL) er en kronisk lungesygdom, som er kendetegnet ved luftvejsobstruktion. Alle patienter med relevante symptomer, som har været udsat for kendte risikofaktorer for udvikling af KOL, bør gennemgå diagnostisk evaluering. En KOL-diagnose er baseret på spirometri, hvor en FEV1/FVC < 0.70 bekræfter diagnosen (spirometrisk sværhedsgrad). Det er af afgørende betydning, at KOL diagnosticeres korrekt, således at en passende behandling kan igangsættes. Alligevel er KOL i høj grad underdiagnosticeret og fejldiagnosticeret. Spirometri er den afgørende lungefunktionstest til anvendelse i diagnosticering og monitorering af KOL, på trods af at spirometri medfører en række problemer. Disse problemer understreger behovet for at søge alternative muligheder inden for lungefunktionstests til patienter med KOL.

Formålet med denne afhandling var todelt. Først havde afhandlingen til formål at undersøge udfordringerne relateret til underdiagnosticering og fejldiagnosticering af KOL. Dernæst var formålet med afhandlingen at undersøge alternative muligheder inden for lungefunktionstests til patienter med KOL. Afhandlingen blev baseret på fire studier, som er repræsenteret i Artikel I-IV. Artikel I-II adresserede afhandlings første formål, og Artikel III-IV adresserede afhandlingens andet formål.

Artikel I undersøgte, hvad der karakteriserede patienter med udiagnosticeret KOL. Deltagere fra the National Health and Nutrition Examination Survey (NHANES) (2007-2012) med spirometribaseret obstruktion (n=1098) blev inkluderet i studiet. Deltagerne blev inddelt i to grupper: Diagnosticerede og udiagnosticerede. Der blev foretaget en række statistiske tests med henblik på at sammenligne 51 faktorer, som karakteriserede de to grupper. Studiet fandt frem til, at deltagerne uden en KOL-diagnose var kendetegnet ved bedre lungefunktion og bedre helbred generelt.

Artikel II undersøgte årsager til fejldiagnosticering af KOL gennem et narrativt review. Der blev foretaget en litteratursøgning i PubMED, EMBASE og Cinahl. Efter en grundig reviewproces blev 73 artikler inkluderet i studiet. Informationen fra de 73 artikler blev sammenfattet i fem temaer, som beskrev årsager til fejldiagnosticering af KOL. Det blev konkluderet, at årsagerne til fejldiagnosticering først og fremmest var knyttet til anvendelsen af spirometri.

Artikel III havde til formål at forbedre spirometri-baseret diagnostiering af KOL ved at justere grænseværdien for præ-bronkodilaterende spirometri. Deltagere fra NHANES (2007-2012), som havde gennemgået post-bronkodilaterende spirometri (n=680), blev inkluderet i studiet. Den præ-bronkodilaterende grænseværdi blev varieret, mens nøjagtighed, sensitivitet, specificitet, negativ prædiktiv værdi og positiv prædiktiv værdi blev udregnet. Resultaterne af studiet viste, at en justering af grænseværdien fra 0.70 til 0.66 forbedrede klassificeringsraten og derved potentielt begrænsede fejlklassificeringen af KOL.

Artikel IV havde til formål at validere SPOT-testen, som er en ny lungefunktionstest tiltænkt patienter med KOL. Patienter med KOL (n=14) blev inkluderet i studiet på Lungemedicinsk Ambulatorium, Aalborg Universitetshospital. Deltagerne gennemførte en række lungefunktionstests, herunder SPOT-testen og en diffusionstest (DLCO). Pearson's korrelationskoefficient blev anvendt til at udregne korrelationen mellem SPOT-testen og DLCO. Studiet fandt en signifikant korrelation mellem SPOT og DLCO, hvilket fremhæver SPOT-testens potentiale som en fremtidig lungefunktionstest til patienter med KOL.

Det kan konkluderes, at diagnosticering af KOL er problematisk. Patienter med udiagnosticeret KOL synes at være karakteriseret af bedre respiratorisk helbred end patienter med en diagnose. Den omfattende underdiagnosticering af KOL kan til dels tilskrives, at respiratoriske symptomer er milde i de tidlige stadier af KOL. Der er mange årsager til fejldiagnosticering af KOL. Disse årsager er først og fremmest knyttet til spirometri, som er den primære lungefunktionstest inden for KOL. Spirometri er associeret med en række bias, og især den spirometriske grænseværdi er omdiskuteret og en vigtig årsag til fejldiagnosticering. En justering af grænseværdien for præ-bronkodilaterende spirometri fra 0.70 til 0.66 kan begrænse misklassificeringen af KOL og dermed forbedre diagnosticeringen. En sådan justering anses dog ikke som værende tilstrækkelig, og der er derfor et behov for alternative lungefunktionstests inden for KOL-området. SPOT-testen synes lovende inden for diagnosticeringen af KOL. Der er dog behov for yderligere studier, som kan undersøge testens validitet og fremtidige rolle inden for diagnosticeringen og monitoreringen af KOL.

PREFACE

This PhD thesis has been submitted for assessment in fulfillment of the PhD degree at the Department of Health Science and Technology, Aalborg University, Denmark. The thesis presents the work that has been accomplished during the course of the PhD starting January 2014. The PhD was supervised by Ole K. Hejlesen.

The PhD was conducted in collaboration with the respiratory diseases clinic at Aalborg University Hospital, Denmark. Moreover, the PhD student has worked extensively with collaborators from the EU-project eWALL, which sponsored the PhD study. This international collaboration led to a number of publications that are not included in the thesis.

The thesis is based on four studies conducted during the PhD study. These four studies have resulted in four articles, which are presented in the thesis. In addition, the thesis includes an introduction and background in which the research field is presented. Moreover, the thesis includes a discussion of the presented work, future perspectives, and conclusions.

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First, I would like to thank my supervisor Ole K. Hejlesen for his supervision throughout my PhD journey. Ole's profound knowledge, positivity, creativity, and continuous support have been essential for my ability to fulfill my PhD.

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PUBLICATION LIST

THESIS PUBLICATIONS

Paper I
Hangaard, Stine; Kronborg, Thomas; Hejlesen, Ole (2018)
Characteristics of patients with undiagnosed chronic obstructive pulmonary disease based on post-bronchodilator spirometry data
Accepted in Respiratory Care

Paper II
Hangaard, Stine; Helle, Tina; Nielsen, Carl; Hejlesen, Ole K. (2017)
Causes of misdiagnosis of chronic obstructive pulmonary disease: A systematic scoping review
Published in Respiratory Medicine, vol. 129, pp. 63-84

Paper III
Kronborg, Thomas; Hangaard, Stine; Cichosz, Simon Lebech; Hejlesen, Ole (2018)
Increased accuracy after adjustment of spirometry threshold for diagnosing COPD based on pre-bronchodilator FEV1/FVC
Accepted in Respiratory Care

Paper IV
Hangaard, Stine; Kronborg Thomas; Redke Finn; Nielsen, Carl; Hejlesen, Ole
A new pulmonary function test for COPD measuring the oxygen transfer characteristics of the lung: A proof of concept study
Intended for submission to European Respiratory Journal

RELATED PUBLICATIONS

Hangaard, Stine; Kronborg, Thomas; Hejlesen, Ole (2018)
Feno: a potential biomarker in COPD?
Proceedings of MIE2018, April 24-26, Göteborg, Sweden

Schaarup, Clara; Hangaard, Stine; Hejlesen Ole K. (2016)
Cognitive walkthrough - an element in system development and evaluation: experiences from the eWALL telehealth system
Published in Procedia Computer Science, vol. 100, pp. 539-546
Conference on ENTERprise Information Systems / International Conference on Project MANagement / Conference on Health and Social Care Information Systems and Technologies, CENTERIS / ProjMAN / HCist - Porto, Portugal

Schaarup, Clara; Hangaard, Stine; Hejlesen, O (2016)
Participatory heuristic evaluation leads to extensive changes in the functionalities of the eWall telehealth system
Published in European Journal of Epidemiology, vol. 31, suppl. 1, p. 172

Schaarup, Clara; Pape-Haugaard, Louise; Hangaard, Stine Veje; Mihovska, Albena; Hejlesen, Ole (2016)
Participatory heuristic evaluation of the first iteration of the eWALL interface application
Proceedings of Wireless VITAE, International Conference on Wireless Communications, Vehicular Technology, Information Theory and Aerospace & Electronic Systems - Hyderabad, India

Hangaard, Stine; Schaarup, Clara; Hejlesen, Ole (2016)
Participatory heuristic evaluation of the second iteration of the eWALL interface application
Proceedings of MIE2016 at HEC2016, 28 August-2 September 2016, Munich, Germany

Schaarup, Clara; Pape-Haugaard, Louise; Hangaard, Stine Veje; Mihovska, Albena; Hartvigsen, Gunnar; Hejlesen, Ole (2015)
Using participatory heuristic evaluation as a collaborative backbone in large-scale projects: preliminary experience from the eWALL EU-project
Proceedings of the 13th Scandinavian Conference on Health Informatics, SHI, 15-17 June 2015, Tromsø, Norway

Hangaard, Stine Veje; Bonderup, Morten Algy; Lilholt, Pernille Heyckendorff; Johansen, Mette Dencker; Hejlesen, Ole (2014)
Instructional video reduces errors in home blood pressure management
Proceedings of MIE2014, 31 August-3 September 2014, Istanbul, Turkey

Hæsum, Lisa Korsbakke Emtekær; Nielsen, G; Hangaard, Stine Veje; Hejlesen, Ole; Dinesen, Birthe (2012)
Identification of heart patients' everyday need: Based on user-driven innovation
Proceedings of Global Telemedicine and eHealth Updates : Knowledge Resources, 18-20 April 2012, Luxembourg

Bonderup, Morten Algy; Hangaard, Stine Veje; Lilholt, Pernille Heyckendorff; Johansen, Mette Dencker; Hejlesen, Ole (2012)
Patient support ICT tool for hypertension monitoring
Proceedings of MIE2012, 26-29 August 2012, Pisa, Italy

Bonderup, Morten Algy; Hangaard, Stine Veje; Lilholt, Pernille Heyckendorff, Johansen, Mette Dencker; Hejlesen, Ole K. (2011)
A pilot assessment of why patients choose not to participate in self-monitoring oral anticoagulant therapy
Proceedings of MIE 2011, 23rd International Conference of the European Federation for Medical Informatics, 28-31 August 2011, Oslo, Norway

ABBREVIATIONS

ATS: American Thoracic Society

CAT: COPD Assessment Test

COPD: Chronic obstructive pulmonary disease

DLCO: Diffusion capacity of the lung for carbon monoxide

ERS: European Respiratory Society

FEV1: Forced expiratory volume in 1 second

FRC: Functional residual capacity

FVC: Forced vital capacity

GOLD: Global Initiative for Chronic Obstructive Lung Disease

LLN: Lower limit of normal

mMRC: The Modified British Medical Counsil (MMRC)

NHANES: National Health and Nutrition Examination Survey

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RV: Residual volume (RV)

SPOT: Simple Pulmonary Oxygen Transfer

TLC: Total lung capacity

TLCO: Transfer factor of the lung for carbon monoxide

VC: Vital capacity

WHO: The World Health Organization

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CHAPTER 1: INTRODUCTION

1.1 RATIONALE FOR THE PHD STUDY

Correct and efficient diagnosis and monitoring are essential for the institution of treatment of COPD. However, COPD is often underdiagnosed and misdiagnosed. The complexity of COPD should not be underestimated, and COPD is challenging to diagnose correctly and monitor efficiently. The challenges related to underdiagnosis and misdiagnosis of COPD need further exploration with an eye toward improving COPD diagnosis.

An issue relating to the diagnostic challenges is the lack of an ideal pulmonary function test. The most commonly used pulmonary function test in COPD is spirometry. However, spirometry proves problematic. Although a COPD diagnosis should always be confirmed based on post-bronchodilator spirometry FEV1/FVC, this ideal is not always implemented in clinical practice. Based on the challenges linked to spirometry, one may consider alternative pulmonary function tests for the diagnosis and monitoring of COPD.

CHAPTER 2: BACKGROUND

This chapter describes COPD and its consequences at a societal level as well as at an individual level. Moreover, the diagnostic process of COPD and the challenges related to underdiagnosis and misdiagnosis are presented. Pulmonary function testing and COPD monitoring are also described.

2.1 SOCIOECONOMIC CONSEQUENCES OF COPD

Chronic obstructive pulmonary disease (COPD) is a major burden to patients and society. The magnitude of this burden is unclear as the global prevalence of COPD is hard to verify, mainly due to underdiagnosis and disagreement on the spirometry threshold for defining COPD (1). Moreover, data on prevalence rates and incidence rates from various countries are lacking (1,2), and the existing predictive data vary in quality (3). It has been estimated that approximately 328 million people have COPD on a worldwide scale. Various studies of COPD prevalence shows prevalence values ranging from 4.5% to 21.5% (1). It is assumed that the prevalence of COPD is approximately 10%. The prevalence increases with age, and the prevalence for people >70 years old is approximately 15% for women and 20% for men (2).

Globally, COPD has been ranked the third leading cause of death (4). The COPD mortality rate in Europe is approximately 18 per 100,000 inhabitants per year (2). However, it should be mentioned that the COPD mortality data may be biased by the underdiagnosis of COPD. Moreover, when COPD is the main cause of death, it may not always be recognized as such (5).

COPD represents a major economic burden, mainly due to exacerbations (5). In Europe, the average COPD admission rate is approximately 200 per 100,000 people per year. More than 50% of patients with COPD who have been admitted due to exacerbation are readmitted within a year (2). The total cost of respiratory diseases within the EU is estimated to be approximately 6% of the total health care budget. Of the cost related to respiratory diseases, 56% (38.6 billion euros) is spent on COPD. In the United States, the direct costs of COPD account for an estimated $29.5 billion, whereas the indirect costs account for an estimated $20.4 billion (5).

2.2 COPD CHARACTERISTICS

COPD is defined as a chronic lung disease that is characterized by persistent airflow limitation and respiratory symptoms (3). The airflow limitation is caused by a blend of small airways disease and parenchymal destruction, often referred to as chronic bronchitis and emphysema, respectively. Inflammatory processes cause narrowing of the small airways, destruction of lung parenchyma, and structural changes of both the small airways and the alveoli. These structural changes cause gas trapping, airflow limitation, hyperinflation, and gas exchange abnormalities (3,5,6).

COPD is caused by exposure to noxious particles and gases (3). The primary cause of COPD is tobacco smoke. Approximately 40-50% of smokers will develop COPD (2). Other factors such as occupational exposure, social status, pollution, environmental, and genetic factors also add to the risk of developing COPD. Moreover, other respiratory diseases such as asthma, chronic bronchitis, and severe respiratory infections during childhood add to the risk of developing COPD (2,3). However, tobacco smoke remains the primary cause of COPD, accounting for approximately 75% of cases (2).

The symptoms of COPD include cough, dyspnea, overproduction of mucus, wheezing, and chest tightness (2,3). In the later stages of COPD, fatigue and weight loss may occur. Comorbidities are common among patients with COPD and may add to the overall severity of the disease. The most common comorbidities include anxiety, depression, ischemic heart disease, osteoporosis, and lung cancer (2).

COPD is characterized by episodic exacerbations during which the respiratory symptoms worsen (2). Bacteria and viruses are the most common causes of exacerbations. Exacerbations may accelerate the progression of COPD, and these episodes thus have a long-lasting negative effect on the health status of patients with COPD. Moreover, the risk of dying is increased among patients who suffer from exacerbations. There are presumably no current biomarkers that predict COPD exacerbations efficiently, although it is highly relevant to identify exacerbations so that they can be prevented or treated at an early stage (2,7). Bronchodilators remain the primary treatment for exacerbations (7).

The goals of COPD treatment are many and include reduction of lung function decline, prevention of exacerbations, reduction of hospitalizations, reduction of mortality, and improvement of quality of life and exercise tolerance (8). The management of COPD includes monitoring, reduction of risk factors, stable disease management, and exacerbation management (2). Smoking secession is essential for

patients who smoke. Moreover, physical exercise plays an important role in the management of COPD, as it reduces respiratory symptoms, reduces anxiety/depression, and improves physical fitness and quality of life in patients with COPD (9). The medical management includes treatment with bronchodilators and inhibitors of inflammation. Severely ill patients may be treated with oxygen therapy (2). Treatment can improve quality of life, functionality, and life expectancy, as well as decrease the level of symptoms (10).

2.3 COPD DIAGNOSIS

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), a diagnosis of COPD should be considered in every patient suffering from dyspnea, chronic cough, or production of sputum who has been exposed to COPD risk factors such as cigarette smoke or environmental pollutants. The primary element in COPD diagnosis is the spirometry assessment. A post-bronchodilator forced expiratory volume in 1 second/forced expiratory volume (FEV1/FVC)<0.7 confirms COPD according to the GOLD definition (5). However, the American College of Physicians (ACP), the American College of Chest Physicians (ACCP), the American Thoracic Society (ATS), and the European Respiratory Society (ERS) define COPD as airflow limitation that is not fully reversible (11,12). Moreover, they prefer to use FEV1/FVC below the statistically defined lower fifth percentile of predicted normal values, aka the lower limit of normal (LLN), as the decisive threshold for COPD (2). One may assume that this disunity regarding the diagnostic threshold may lead to diagnostic confusion among primary care physicians, who typically perform the diagnostic evaluation.

Spirometry is also an essential element in assessing the severity of COPD, as COPD is classified into spirometry-defined severity stages. GOLD and the ATS/ERS have not reached a consensus on how to distinguish among the severity stages (3,12). The four GOLD stages are most commonly used. However, the ATS and the ERS argue that five stages are appropriate when assessing the severity of COPD. Table 1 presents the severity stages as defined by GOLD and the ATS/ERS, respectively. The predicted reference values are based on height, age, sex, and race (3).

Stage	ATS/ERS	GOLD
Mild	FEV1/VC<5th percentile of predicted and FEV1≥70% of predicted	FEV1/FVC<0.7 and FEV1>80% of predicted
Moderate	FEV1/VC<5th percentile of predicted and FEV1=60-69% of predicted	FEV1/FVC<0.7 and 50%≤FEV1<80% of predicted
Moderately severe	FEV1/VC<5th percentile of predicted and FEV1=50-59% of predicted	N/A
Severe	FEV1/VC<5th percentile of predicted and FEV1=35-49% of predicted	FEV1/FVC<0.7 and 30%≤FEV1<50% of predicted
Very severe	FEV1/VC<5th percentile of predicted and FEV1<35% of predicted	FEV1/FVC<0.7 and FEV1<30% of predicted

Table 1: The criteria for assessing COPD severity according to the ATS/ERS and GOLD (2,3,12). Abbreviations are as follows: ATS: American Thoracic Society; ERS: European Respiratory Society; GOLD: Global Initiative for Chronic Obstructive Lund Disease; FEV1: forced expiratory volume in 1 second; VC: vital capacity; FVC: forced vital capacity.

Although spirometry remains the key element in diagnosis of COPD, it should not be the only approach used in diagnosing or assessing COPD. GOLD and the ATS/ERS agree that the patient's symptoms and medical history should be included in the assessment as well (3,12). Two tests are often used to assess the symptoms: the Modified Medical Research Council (mMRC) questionnaire (13) and the COPD Assessment Test (CAT)(14). The mMRC questionnaire is a simple tool for assessing dyspnea (13), whereas the CAT is an 8-item questionnaire that assesses the impact of COPD on a patient's life (14).

The risk of exacerbations should also be taken into account in the combined assessment of COPD. Finally, additional assessments may be considered, including imaging, testing of lung volumes, testing of the diffusion capacity of the lung, pulse oximetry, arterial blood gas measurement, assessment of physical activity, and exercise tests (3).

A correct COPD diagnosis is essential for the course of treatment. A false positive diagnosis may lead to unnecessary side effects and costs, whereas a false negative diagnosis may lead to a lack of relevant treatment as outlined in Figure 1 (15,16). However, it has been estimated that more than 50% of the 24 million Americans with COPD are either misdiagnosed or undiagnosed (17).

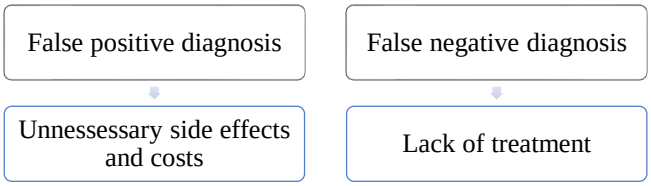

Figure 1: Indications for correct diagnosis of COPD.

Diagnosis of COPD is challenging. This challenge may be seen as two-sided as it includes underdiagnosis as well as misdiagnosis. As described, numerous patients with COPD remain unidentified accounting for the comprehensive underdiagnosis of COPD. Moreover, when a patient is actually identified and undergoes diagnostic evaluation, errors occur, and patients are misdiagnosed. Both the challenge of underdiagnosis and misdiagnosis will be described in the succeeding sections.

2.3.1 UNDERDIAGNOSIS

Early diagnosis of patients with COPD is warranted to prevent disease progression, reduce exacerbations, and reduce healthcare costs (1,5,18). However, COPD remains heavily underdiagnosed (1,19,20). Patients in the early stages of COPD may benefit significantly from treatment, as it seems that the most rapid decline in lung function in COPD occurs in the moderate stage (21). Smoking cessation reduces lung function decline the most at the earlier stages of COPD (22). Thus, it is highly important that COPD is identified early to enable early diagnosis. In this way, bronchodilator treatment and smoking cessation may be initiated at an earlier disease stage potentially altering the progression of COPD and improving quality of life (21,22).

The underdiagnosis of COPD may be caused by a variety of factors, including lack of knowledge and awareness of the disease, lack of believe in the effect of treatment, underuse of spirometry, limited respiratory symptoms, etc. (21,23). Limited knowledge of COPD and attention to symptoms may cause a delay of COPD diagnosis and thereby cause underdiagnosis. It is, of course, difficult to determine a diagnosis without any obvious symptoms, which may cause a diagnostic delay until the disease has progressed to a more severe level (23). Some patients with clinically relevant COPD do not have any respiratory symptoms. For instance, a study by Akamatsu et al. (2009) found that 52% of their subjects with a COPD diagnosis had never complained of respiratory symptoms (24).

It is considered highly relevant to reveal the characteristics of patients with COPD who remain undiagnosed. Such a revelation would potentially optimize the chances of identifying and diagnosing patients with undiagnosed COPD. A few studies have explored factors characterizing patients with undiagnosed COPD. However, such studies have been inconsistent when it comes to basing their results on post-bronchodilator spirometry (25,26).

2.3.2 MISDIAGNOSIS

When a potential case of COPD is identified and the diagnostic process is completed, further challenges arise. The misdiagnosis of COPD is common, and it seems to be caused by a multitude of factors. There is ongoing discussion about the ideal spirometry threshold to apply in the diagnosis of COPD. The fixed threshold of 0.70 has been criticized for leading to misdiagnosis of COPD (27,28). In their most recent recommendations, GOLD recognizes that the fixed threshold leads to more frequent diagnosis among older patients and less frequent diagnosis among younger patients. Moreover, spirometry remain underused (29,30), and the spirometry test may be biased (31). Thus, the causes of misdiagnosis of COPD are multifaceted, which calls for an overview of these causes.

The diagnostic guidelines are not always followed. Studies have shown that bronchodilators are underused (30,32) although diagnostic guidelines clearly describe that COPD diagnosis should always be based on post-bronchodilator spirometry (3). Arne et al. (2010) found that spirometry data were accessible for only 59% of subjects with a recent diagnosis of COPD. Post-bronchodilator spirometry data were accessible for only 45% of the same group of subjects. Out of these 45% of subjects with accessible post-bronchodilator spirometry data, 34% had a post-bronchodilator FEV1/FVC>0.70 (30). These results mirror the findings of Miravittles et al. (2007) who found accessible post-bronchodilator spirometry data in 32% of their subjects (32). Obviously, this underuse of bronchodilators represents a diagnostic challenge as well. This challenge calls for an optimization of pre-bronchodilator-based diagnosis of COPD.

2.4 PULMONARY FUNCTION TESTS

Pulmonary function tests are essential in the diagnosis, monitoring, and management of patients with respiratory diseases such as COPD (33). A variety of pulmonary function tests may be used to diagnose COPD and assess the severity of the disease. In addition to pulmonary function tests, COPD severity may also be assessed using

questionnaires, imaging, physical tests, etc. (3). Spirometry and the testing of diffusion capacity of the lung for carbon monoxide are described in detail in the succeeding sections.

2.4.1 SPIROMETRY

Spirometry is the most commonly used pulmonary function test. It measures how a subject inhales or exhales volumes of air (3,34). In COPD, spirometry is used to measure airflow limitation in a noninvasive manner. Spirometry typically measures the volume of air that a subject can exhale (FVC) and the volume of air that a subject can exhale in the first second of exhalation (FEV1). The exhalation should be as forcefully as possible and start after complete inhalation. Figure 2 illustrates the flow of the FEV1/FVC maneuver. The maneuver is repeated three times (34).

Figure 2: The FEV1/FVC maneuver (34).

Most often, the ratio of FEV1/FVC is calculated (3,34). The results of the spirometry test are compared to reference values, which are based on sex, height, and race (3). A variety of different spirometers may be used. Continuous quality control of equipment and calibration is recommended. The result of a spirometry test will depend on a variety of factors, including both personal and technical aspects. The subject and the person who performs the examination must cooperate with each other. The subject should be verbally encouraged during the examination in an enthusiastic manner using both encouraging phrases and body language (34).

An acceptable spirometry test must have a satisfactory start and a satisfactory end. The subject must have understood the instructions and performed the maneuver correctly. Seven conditions must be met for a test to be considered acceptable, as illustrated in Table 2 (34).

Conditions for acceptable spirometry
No unsatisfactory start of exhalation (e.g., hesitation)
No cough affecting the measurement
No early termination of exhalation
No Valsalva maneuver or hesitation during the maneuver
No leak
No obstructed mouthpiece
No extra breath during the maneuver

Table 2: Seven conditions for acceptable spirometry, the FEV1/FVC maneuver (34).

The repeatability criteria require three acceptable FVC maneuvers for an adequate spirometry test. The difference between the highest and the second highest FVC should be ≤0.15 L. The difference between the highest and the second highest FEV1 should also be ≤0.15 L. If the first three maneuvers fail to meet these repeatability criteria, more maneuvers should be completed. However, the subject should usually not undergo more than eight tries (34).

A variety of factors may bias the spirometry test, including various technical aspects, socioeconomic factors, occupation, gender, body size, age, smoking status, and ethnicity (35). Spirometry is inadequate as the only pulmonary function test in COPD, and spirometry alone should not be used to monitor disease progression or the impact of treatment (6).

2.4.2 DIFFUSION CAPACITY OF THE LUNG FOR CARBON MONOXIDE

The diffusion capacity of the lung for carbon monoxide (DLCO) is also known as the transfer factor (TLCO). DLCO measures the ability of the airways to exchange gases across the alveolar-capillary membrane. This ability is determined by structural as well as functional properties (illustrated in Tables 3 and 4) (36). As previously described, COPD is characterized by parenchymal destruction (emphysema), where the surface area available for diffusion is decreased due to structural changes of the lung. When the severity of COPD increases due to more pronounced emphysema, DLCO will decrease (37).

Structural properties
Lung gas volume
Path length for diffusion
Thickness of the alveolar-capillary membrane
Area of the alveolar-capillary membrane
Airway closure
The hemoglobin volume in the capillaries that supply the alveoli

Table 3: Structural properties determining the gas exchange capacity of the lung

Functional properties
Levels of ventilation
Levels of perfusion
The uniformity distribution of ventilation vs. perfusion
Composition of alveolar gas
Membrane diffusion characteristics
Properties of hemoglobin in the alveolar capillaries
The tension of carbon monoxide vs. oxygen in the gas exchange within the alveoli

Table 4: Functional properties determining the gas exchange capacity of the lung

All systems used for DLCO are based on the same principles. The system has a source of test gas containing 10% helium and 0.3% carbon monoxide (33,36). The test measures inhaled and exhaled volume, and the concentration of carbon monoxide and tracer gas, respectively. A variety of procedures exists to ensure quality control of the systems (36).

The most commonly used breathing technique for determination of DLCO is the single-breath technique (DLCO SB) (38,39). Prior to the test, the patients should be instructed thoroughly in all aspects of the test. The subject must be seated comfortably and wear a nose clip. The inspiratory maneuvers start with the patient performing tidal breathing to ensure that the mouthpiece and nose clip are working properly. The DLCO maneuver starts with the patient performing an unforced exhalation to residual volume (RV). The exhalation period should not exceed 12 seconds. The patient then inhales test gas rapidly to total lung capacity. Next, the patient holds his/her breath for 10±2 seconds. The breath hold is followed by an exhalation in which the lungs should be instantaneously emptied (Figure 3) (36).

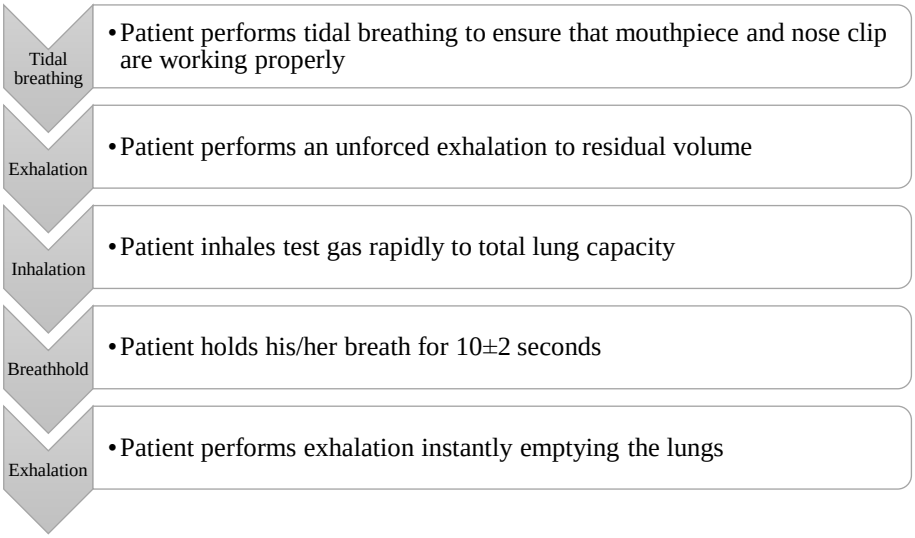

Figure 3: The DLCO test procedure (36).

To ensure proper washout of test gas from the lungs, the second test should not be performed until at least four minutes after the first test. Moreover, a variety of criteria for acceptability should be met as illustrated in Table 5. The repeatability criteria is defined as at least two acceptable measurements that lie within 2 $mL \cdot min^{-1} \cdot mmHg^{-1}$ (0.67 $mmol \cdot min^{-1} \cdot kPa^{-1}$). The mean of the results of at least two acceptable maneuvers should be reported. There are currently no reliable reference values for DLCO (36).

Criteria for acceptability, DLCO
VI should be ≥90% of the largest VC of the test session. Alternatively, VI should be ≥85% of the largest VC of the same session plus VA within 200 mL or 5% of the largest VA from other acceptable DLCO maneuvers
85% of the test gas should be inhaled in <4 seconds
A stable breath hold should be maintained for 10 ± 2 seconds. No leaks or Valsalva or Müller maneuvers
The collection of the sample should be completed within 4 seconds

Table 5: Summary of the criteria for acceptability of DLCO (36). VI: Inspiratory volume; VC: Vital capacity; VA: Alveolar volume

DLCO is useful as a supplemental pulmonary function test in the diagnosis of COPD. Moreover, DLCO is useful in disease monitoring, as changes in DLCO suggest changes in lung function (36). However, DLCO is a complex test that requires

advanced equipment (38,40). DLCO is associated with bias from a variety of factors, including gender, height, ethnic origin, age, hemoglobin, and carboxyhemoglobin (35). Moreover, a study by Sansores et al. found that DLCO varied significantly during the menstrual cycle (41). Another disadvantage of DLCO is the fact that the test is linked to many technical sources of variability including equipment, software, test procedures and gases, inspired oxygen pressure, reference equations, and atmospheric conditions (35,42). In addition, the variability of DLCO is high (43).

In summary, there are advances and challenges linked to DLCO as well as spirometry. The tests provide insight into two different aspects of the respiration including diffusion capacity and airflow. The equipment used for spirometry measurement is fairly simple, whereas the equipment used for DLCO is quite complex. Both tests are associated with a multitude of bias, which calls for alternative strategies in COPD pulmonary function testing.

2.5 COPD MONITORING

It is essential to follow the progression of COPD in order to minimize or avoid exacerbations (7). However, it is not possible to monitor patient symptoms on a regular basis at a hospital setting. Various studies have used telemedicine as an alternative to conventional treatment (44–46). The World Health Organization (WHO) defines telemedicine as follows:

> "The delivery of health care services, where distance is a critical factor, by all health care professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evaluation, and for the continuing education of health care providers, all in the interests of advancing the health of individuals and their communities"(47).

Various telemedicine studies have used different telemedicine setups in the monitoring and treatment of patients with COPD aiming to improve quality of life, limit exacerbations, minimize hospital admissions, and reduce healthcare costs, etc. Telemedicine seems to have a positive effect on quality of life and number of visits to the emergency department and the hospital (44). However, the evidence within the area of telemedicine is weak (46), and further research is requested (44–46).

The published literature on telemedicine trials shows a great variety in the technologies used for the intervention. Spirometry is often not included, and

more secondary parameters such as blood saturation, weight, and health-related questions are utilized instead (44,45). One may assume that spirometry is excluded from the trials because it is too complicated for the test subjects to perform the spirometry test without assistance from a healthcare professional (34). One may also assume that the ideal COPD telemedicine setup must include a pulmonary function test. A pulmonary function test may have the potential of optimizing the chances of predicting exacerbations so that early treatment can be initiated. However, there are currently no reliable biomarkers that are able to predict exacerbations (7). This lack of reliable biomarker to predict exacerbations emphasizes the need for an alternative pulmonary function test that may able to predict exacerbations in a telemedicine setting.

2.6 SUMMARY OF INTRODUCTION

In this chapter, COPD and its individual and societal consequences were outlined. Moreover, COPD diagnosis and the challenges of underdiagnosis and misdiagnosis were highlighted. The underdiagnosis and misdiagnosis of COPD is severe even though a correct diagnosis is essential for the course of treatment. More profound knowledge regarding characteristics of undiagnosed patients and causes of misdiagnosis of COPD would potentially contribute to improve diagnosis of COPD. Several pulmonary function tests exist aiming to measure i.e., airflow and the diffusion capacity of the lung. However, the existing pulmonary function tests are often complex and biased by a variety of factors. These circumstances call for alternative approaches in COPD pulmonary function testing.

CHAPTER 3: AIMS

This chapter presents the overall aims of the thesis and the research objectives of the thesis papers.

3.1 THESIS AIMS

The overall aim of the thesis is twofold, as the thesis seeks to cover two areas. First, the thesis seeks to gain deeper insight into the problem area. It is well recognized that COPD is underdiagnosed as well as misdiagnosed. However, the causes of these diagnostic challenges are less clear. Hence, the first aim of the thesis is ***to explore the challenges of underdiagnosis and misdiagnosis of COPD.***

Second, the thesis seeks to explore potential solutions to the challenges identified in the first part of the thesis by focusing on pulmonary function testing. Spirometry remains the key pulmonary function test in COPD. However, spirometry is associated with a multitude of challenges. Hence, the second aim of the thesis is ***to explore alternatives to existing methods in COPD pulmonary function testing***.

Four individual studies represented in four individual papers (I-IV) seek to meet the aims of the thesis. Paper I-II address the first thesis aim, whereas Paper III-IV address the second thesis aim. The thesis aims and each of their associated papers and research objectives are illustrated in Figure 4.

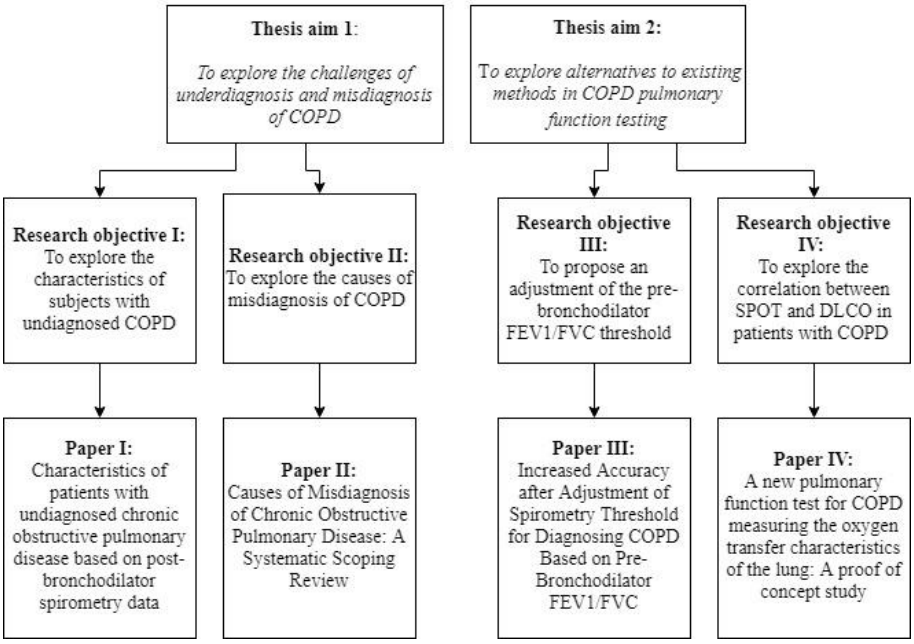

Figure 4: The thesis aims and their associated research objectives and papers.

CHAPTER 4. SUMMARY OF PAPERS

This chapter provides a summary of the work conducted in each of the thesis papers focusing on the methods and results.

4.1 PAPER I

Title: Characteristics of patients with undiagnosed chronic obstructive pulmonary disease based on post-bronchodilator spirometry data

Due to a comprehensive underdiagnosis of COPD, it is highly relevant to obtain a more profound understanding of the factors that characterize patients with undiagnosed COPD. Therefore, this study aimed to explore the characteristics of subjects with undiagnosed COPD.

The study included (n=30,442) subjects from the National Health and Nutrition Examination Survey (NHANES) dataset (2007-2012) (48,49). Subjects without spirometry-based obstruction and subjects who had not responded to questions regarding existing COPD diagnosis were excluded. These criteria resulted in a final sample of n=1098 subjects. These subjects had spirometry-based obstruction (FEV1/FVC<0.7 or LLN). A previous COPD diagnosis was present in n=93 subjects, and no previous COPD diagnosis was present in n=1005 subjects.

COPD diagnosis was determined solely based on spirometry. The diagnosed subjects were defined by a FEV1/FVC<0.7 or LLN combined with a positive response to at least one of the questions: "*Have you ever been told by a doctor or other healthcare professional that you have 1) chronic bronchitis, or 2) emphysema*?" The undiagnosed subjects were defined by a FEV1/FVC<0.7 combined with a negative response to the questions: *"Have you ever been told by a doctor or other healthcare professional that you have 1) chronic bronchitis, or 2) emphysema?"*

The data was merged and processed using MATLAB (The MathWorks Inc., Natick, Massachusetts, United States), and SPSS (IBM Corp., IBM SPSS Statistics, Armonk, NY, USA) was used for the statistical analyses. Table 6 illustrates the use of statistical tests for the different types of variables.

Test	Type of variable
Pearson's chi-squared test	Nominal variables
Mann-Whitney U test	Ordinal variables
Mann-Whitney U test	Continuous variables that lacked normality or homogeneity of variances
T-test	Continuous variables with normality and homogeneity of variance

Table 6: Overview of the statistical tests used for each type of variable

Fifty-one potential factors characterizing underdiagnosed COPD were tested. Bonferroni correction was applied in order to correct for the accumulated probability for type 1 error, resulting in a significance level of $p<0.001$ ($p<0.05/51$).

The analysis showed that 13 out of 51 factors characterizing undiagnosed COPD were statistically significant ($p<0.001$). The significant factors are presented in Table 7.

Factors characterizing subjects with undiagnosed COPD (p<0.001)
Less phlegm
Less wheezing
Less chest pain
Less shortness of breath on stairs/inclines
Fewer work/school days lost to wheezing
Less sleep disturbance due to wheezing
Less difficulty socializing
Less depression
Less likely to ever have had asthma
Less likely to have current asthma
Higher annual household income
Higher FEV1
Higher FVC

Table 7: Statistically significant factors characterizing subjects with undiagnosed COPD (p<0.001).

In conclusion, the results of Paper I showed that a better health condition characterized subjects with undiagnosed COPD.

4.2 PAPER II

Title: Causes of misdiagnosis of chronic obstructive pulmonary disease: A systematic scoping review

COPD is highly misdiagnosed. However, to our knowledge, no present study had reviewed the existing literature for causes of misdiagnosis of COPD. Thus, this study aimed to explore the causes of misdiagnosis of COPD and thereby provide an overview of these factors.

A paper by Green et al. (2006) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement served as a guideline for the review (50,51). Green et al. (2006), define scoping overviews as "*comprehensive narrative syntheses of previously published information*" (50). Peer-reviewed papers that explained causes of misdiagnosis of COPD were included in the review. The criteria for inclusion and exclusion are presented in Tables 8 and 9.

Criteria for inclusion
Papers explaining misdiagnosis of COPD
Search period: 1994-2016
English, German, and all Scandinavian languages
Peer-reviewed papers

Table 8: Criteria for inclusion of papers.

Criteria for exclusion
Papers on misdiagnosis due to lack of spirometry in the diagnosing of COPD
Papers on underdiagnosis of COPD due to lack of diagnosing

Table 9: Criteria for exclusion of papers.

A preliminary search gave an overview of the published literature within the area. Next, a systematic search was conducted in Medline (PubMed), EMBASE, and CINAHL. The search was based on the overall search terms "COPD" and "misdiagnosis" supplemented with synonyms, near synonyms, and acronyms. Supplemental literature identified by snowballing was also included.

The review process consisted of multiple steps as illustrated in Figure 5. First, all papers were imported into Refworks (ProQuest LLC) where duplicates were removed. Subsequently, all titles and abstracts were screened. The remaining papers were then

reviewed critically resulting in the final sample of papers.

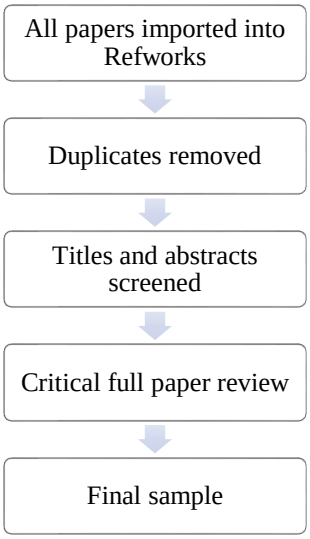

Figure 5: The steps of the review process

The information identified in the literature search was synthesized into themes. Subsequently, the papers were categorized into these themes. The literature search identified 1,865 potentially relevant papers. After the review, 73 papers remained representing the final sample. The final sample revealed five themes explaining causes of misdiagnosis of COPD. The themes are presented in Table 10.

#	Incl. (%)	Theme	Summary	Papers
1	36 (49)	The threshold for defining COPD	The fixed threshold causes overdiagnosis in older subjects and underdiagnosis in younger subjects. LLN is suggested as an alternative threshold. However, LLN may lead to underdiagnosis.	6,20,58–67,27,68–77,28,78–83,52–57
2	15 (21)	Errors made in primary care	Diagnostic mistakes are more often made when a diagnosis is established in primary care compared to a diagnosis by a pulmonary expert.	23,84,93–97,85–92
3	13 (18)	Errors linked to the spirometry test	The quality of spirometry testing is poor. Some patients are unable to perform satisfactory spirometry. Physiological changes may bias the test. Lack of bronchodilators cause misdiagnosis.	57,61,104–106,75,95,98–103
4	10 (14)	Differential diagnoses	Patients with comorbidities are more often misdiagnosed.	23,61,96,107–113
5	8 (11)	Patient-related factors	Various patient-related factors such as sex, ethnicity, drug intake, weight, and smoking may bias the diagnosis.	24,74,91,114–118

Table 10: The five themes, their distribution, and their related papers. Incl. (%)=number of papers included in the theme. Abbreviation: LLN: lower limit of normal.

In conclusion, this study found that the causes of misdiagnosis of COPD are primarily linked to spirometry and to the person performing the diagnosis.

4.3 PAPER III

Title: Increased accuracy after adjustment of spirometry threshold for diagnosing COPD based on pre-bronchodilator FEV1/FVC

Bronchodilators are underused in the diagnosis of COPD. Establishing guidelines for COPD diagnosis based on pre-bronchodilator FEV1/FVC may have the potential of improving COPD diagnosis. This study aimed to quantify the classification rates based on pre-bronchodilator spirometry and to propose an adjustment of the threshold for defining COPD based on pre-bronchodilator spirometry.

The study included subjects from NHANES. Data were merged for 23,433 subjects from NHANES 2007-2012 who had undergone post-bronchodilator spirometry. After excluding subjects based on the exclusion criteria illustrated in Table 11, 680 subjects remained for the analysis.

Exclusion criteria	No. of subjects excluded
No post-bronchodilator data	21,869
<40 years of age	807
Asthma	76
Lung cancer	1

Table 11: Criteria for exclusion from the study and the number of subjects excluded for each of the criteria

A COPD diagnosis was determined based on pre-bronchodilator FEV1/FVC. The pre-bronchodilator diagnosis was then verified as either true or false based on post-bronchodilator FEV1/FVC. The classification rates were assessed by varying the pre-bronchodilator threshold while calculating the accuracy, the specificity, the sensitivity, the negative predictive value, and the positive predictive value. The suggestion for adjustment of the diagnostic threshold for pre-bronchodilator FEV1/FVC was based on accuracy.

The diagnostic accuracy increased from 0.64 to 0.79 when COPD was classified by pre-bronchodilator FEV1/FVC<0.66 instead of pre-bronchodilator FEV1/FVC<0.70. The results are summarized in Table 12.

Pre-bronchodilator FEV1/FVC	**0.70**	**0.66**
Accuracy	0.64	0.79
Sensitivity	1.00	0.75
Specificity	0.10	0.86
Negative predictive value	0.96	0.69
Positive predictive value	0.62	0.89

Table 12: Classification rates based on pre-bronchodilator FEV1/FVC 0.70 and 0.66. The table was adapted and adjusted from Paper III. Abbreviations: FEV1: Forced expiratory volume in 1 second; FVC: Forced vital capacity.

In conclusion, it is suggested that the threshold for defining COPD is adjusted to a pre-bronchodilator FEV1/FVC<0.66. The pre-bronchodilator FEV1/FVC<0.70 threshold has poor classification rates and contributes to misclassification of COPD.

4.4 PAPER IV:

Title: A new pulmonary function test for COPD measuring the oxygen transfer characteristics of the lung: A proof of concept study

COPD is complex and difficult to diagnose and monitor using existing pulmonary function tests such as spirometry and DLCO. These circumstances call for an alternative pulmonary function test. This study aimed to explore the correlation between DLCO and the Simple Pulmonary Oxygen Transfer Test (SPOT test) in order to validate the SPOT test as a future pulmonary function test for COPD.

The SPOT test is a pulmonary function test that is currently under development in collaboration between Aalborg University and Aalborg University Hospital. The SPOT test is based on existing technologies and aims to determine the lung function of patients with COPD based on the principles from DLCO. The SPOT test aims to minimize complexity and bias known from existing pulmonary function tests and measure lung function in a simple and noninvasive manner.

The specific principles of the SPOT test are described in detail in Paper IV included in the full paper version of the thesis. It should, however, be mentioned that the SPOT test remains at a preliminary level, and a profound SPOT technology is yet to be developed.

The study was conducted at Aalborg University Hospital at the hospital respiratory medicine clinic. All subjects signed informed consent forms, and the local ethical committee gave their consent for the study. Clinical staff from the respiratory medicine clinic included subjects ≥18 years of age with an existing diagnosis of COPD. Twenty subjects were included. However, six subjects were excluded due to; measurement error (n=1), lacking signal from pulse oximeter (n=1), FEV1/FVC>0.7 (n=4). Thus, n=14 subjects remained in the final sample.

A trained nurse performed body plethysmography (including spirometry) and DLCO in accordance with existing guidelines (34,36,119). Researchers from Aalborg University performed the SPOT test. The SPOT test was performed twice for each subject.

The results from the two SPOT tests were averaged in the analysis. Pearson's product moment correlation was used to measure the correlation between the SPOT value, DLCO SB (% of predicted), and FEV1 (% predicted). DLCO is known to be biased by smoking (35). Therefore, an additional analysis was performed in which only the n=11 nonsmokers were included.

For all 14 subjects, SPOT correlated with DLCO SB (r=-0.730; p=0.003) (Figure 6). SPOT and FEV1 did not correlate (r=0.194; p=0.507), and DLCO SB and FEV1 did not correlate (r=-0.329; p=0.251). The additional analysis of the 11 nonsmokers also showed that SPOT correlated with DLCO SB (r=-0.755; p=0.007).

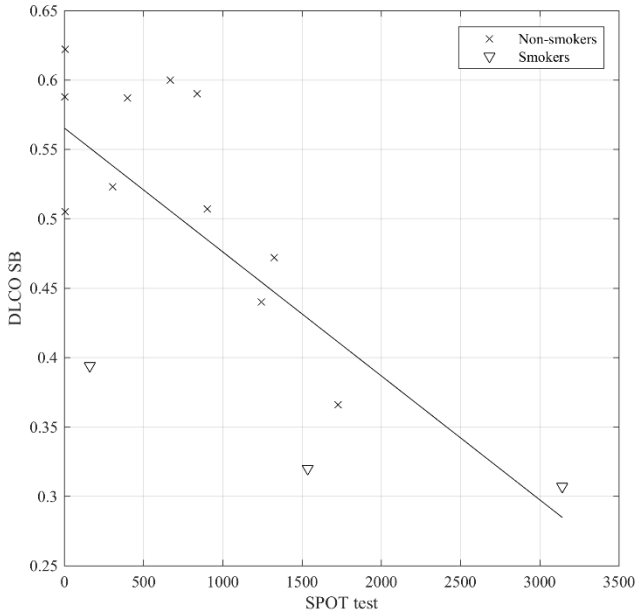

Figure 6: The correlation of the SPOT test and DLCO.

In conclusion, the SPOT test shows promise as a COPD pulmonary function test as it correlated significantly with DLCO SB.

CHAPTER 5: THESIS PAPERS

This chapter presents the papers that constitute the core of the thesis. The full texts of the papers are included in the full version of the thesis.

5.1 PAPER I

Characteristics of patients with undiagnosed chronic obstructive pulmonary disease based on post-bronchodilator spirometry data

Hangaard, Stine; Kronborg, Thomas; Hejlesen, Ole K. (2018)

RESPIRATORY CARE

5.2 PAPER II

Causes of Misdiagnosis of Chronic Obstructive Pulmonary Disease: A Systematic Scoping Review

Hangaard, Stine; Helle, Tina; Nielsen, Carl; Hejlesen, Ole K. (2017)

Published in Respiratory Medicine, vol. 129, pp. 63-84

5.3 PAPER III

Increased Accuracy after Adjustment of Spirometry Threshold for Diagnosing COPD Based on Pre-Bronchodilator FEV1/FVC

Kronborg, Thomas; Hangaard, Stine, Cichosz, Simon Lebech; Hejlesen, Ole

RESPIRATORY CARE

5.4 PAPER IV

A new pulmonary function test for COPD measuring the oxygen transfer characteristics of the lung: A proof of concept study

Hangaard, Stine; Kronborg, Thomas; Redke, Finn; Nielsen, Carl; Hejlesen, Ole

Intended for submission to:

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

CHAPTER 6: DISCUSSION

This chapter begins with a short summary of the main findings of the thesis. The summary is followed by methodological considerations. Subsequently, the results of the thesis papers are discussed. Finally, the chapter provides suggestions for future perspectives.

6.1 SUMMARY OF THE MAIN FINDINGS

This PhD study aimed to explore the challenges of underdiagnosis and misdiagnosis of COPD and to explore alternative methods in COPD pulmonary function testing. Paper I presented characteristics of subjects with undiagnosed COPD. Overall, the undiagnosed subjects were characterized by fewer respiratory symptoms and better health condition than the subjects who had been diagnosed. The study presented in Paper II identified various causes of misdiagnosis of COPD. The causes were mainly linked to spirometry. These findings emphasized the call for further investigation of alternative methods in COPD pulmonary function testing. Hence, the study presented in Paper III aimed to propose an adjustment of the pre-bronchodilator FEV1/FVC threshold for diagnosing COPD with an eye to limiting misclassification. The results of Paper III showed that an adjustment of the threshold from 0.70 to 0.66 resulted in a 15.6% increase in accuracy. However, an adjustment of the threshold does not solve the challenge of misdiagnosis of COPD. An alternative pulmonary test may provide a more long-term solution to the issues represented by pulmonary function testing in COPD. Study IV aimed to explore the correlation between SPOT and DLCO with a view to explore the potential of the SPOT test as an alternative pulmonary function test for COPD. SPOT correlated significantly with DLCO SB (% of expected), and the SPOT test thus shows promising results as a pulmonary function test for COPD.

6.2 METHODOLOGICAL CONSIDERATIONS

Each of the thesis studies have strengths and limitations, which will be elaborated in this section.

6.2.1 PAPER I

Paper I contributed information regarding the characteristics of undiagnosed COPD. A strength of the study presented in Paper I was that a relatively high number of characteristics of undiagnosed COPD were explored. However, additional potential

characteristics such as edema, peptic ulcer, history of lower tract infection, etc. were not explored as they were not included in the NHANES survey.

The study presented in Paper I is limited by the fact that a COPD diagnosis was solely presumed for the subjects who responded positively to whether they had been told that they had emphysema or chronic bronchitis. Thus, some subjects may have answered incorrectly, which would result in an incorrect classification as either undiagnosed or diagnosed. In addition, the study is limited by the fact that the diagnosis is based on spirometry alone. However, these diagnostic limitations were accommodated by using the same procedure for defining COPD as similar studies (25,120). The study had a very high rate of underdiagnosis among the included subjects as 91.53% of the subjects reported no previous diagnosis of COPD. This unusually high rate may partly be explained by the diagnostic criteria selected for the study. However, the high rate may also be explained by the fact that the subjects had only mild respiratory symptoms, hindering an early diagnosis.

Another limitation of the study is that subjects with severe COPD may be less inclined to participate in a survey such as NHANES. Thus, the sample may not represent all COPD severity grades.

6.2.2 PAPER II

Paper II contributed an overview of previously published literature describing causes of misdiagnosis of COPD. A general strength of scoping reviews is that they are particularly useful for allowing synthesizing of comprehensive topics (121). Paper II was conducted based on guidelines provided by Green et al. (2006) and PRISMA to ensure a systematic methodological approach of high quality (50,51). Moreover, Paper II was strengthened by the fact that the second author of Paper I validated the final sample of papers.

A general limitation of scoping reviews is that the papers are not assessed for quality. Thus, the strength of the studies is not taken into account. The search of literature was performed in three medical databases (PubMed, EMBASE, and Cochrane), and the search was restricted in time and language. Thus, it is safe to assume that not all literature describing causes of misdiagnosis of COPD was included in the review.

6.2.3 PAPER III

Paper III contributed a suggestion for adjustment of the pre-bronchodilator threshold for defining COPD. A strength of the study presented in Paper III was that it was

based on data from the NHANES dataset. NHANES has developed comprehensive spirometry standardized procedures assuring high quality spirometry assessments (122).

The study presented in Paper III included only subjects between the ages of 40 and 79 years. Thus, the results of Paper III may not apply to subjects under 40 years of age or to subjects above 79 years of age. Only a few subjects had very severe COPD. One may assume that patients with severe disease are less likely to participate in a comprehensive survey such as NHANES resulting in a less representative sample.

The study diagnosis of COPD was based on spirometry alone, which represents a limitation. COPD ought to be considered in all potential patients with chronic cough, sputum production, dyspnea, and/or history of exposure to COPD risk factors (123). However, the NHANES questionnaires regarding respiratory symptoms were considered insufficient for diagnostic assessment in the study.

6.2.4 PAPER IV

Paper IV contributed a preliminary validation of the SPOT test as a future pulmonary function test for COPD. The study presented in Paper IV was the first to explore the validity of the SPOT test. The study was strengthened by the fact that a trained nurse with exhaustive experience in pulmonary function testing carried out the body plethysmography and the DLCO test.

A limitation of the study was that only 14 subjects were included in the analysis. More subjects would have strengthened the results. Moreover, all data related to the SPOT test were registered manually, which increase the risk of registration errors. The risk of manual error was accommodated by the fact that two researchers always performed the SPOT test.

6.3 DISCUSSION OF RESULTS

The results of the four thesis papers will be discussed in the succeeding sections.

6.3.1 UNDERDIAGNOSIS OF COPD

In line with Paper I, previous publications have explored the characteristics of subjects with undiagnosed COPD. The results of Paper I may be compared to a study by Martinez et al. (2015), which was based on data from NHANES as well. Martinez et al. (2015) identified the following factors characterizing undiagnosed COPD: female

sex, higher age, lower BMI, fewer respiratory symptoms, and higher FEV1 (25). In line herewith, Hvidsten et al. (2010) found that characteristics of subjects with undiagnosed COPD included a more positive self-rated health condition and a better lung function, including respiratory symptoms (124). Santos et al. (2014), Balcells et al. (2015), and Lamprecht et al. (2015) also found that undiagnosed COPD was characterized by less severe disease (15,26,125). The study by Lamprecht et al. (2015) also distinguishes from Paper I, because their undiagnosed subjects were characterized by younger age, male sex, and lower education (15). However, these additional studies treating characteristics of undiagnosed COPD overall agree with the results of Paper I, as subjects with undiagnosed COPD seems to be characterized by better lung function and less severe respiratory symptoms than their undiagnosed counterparts. However, the literature still needs to determine the significance of additional characteristics; including age, educational level, and income. This statement is supported by a review by Han et al. (2015) who found that variables such as education, occupation, and childhood illness are not included in COPD case-finding tools even though they may add value (126).

There seems to be general agreement that the existing evidence base does not support the screening of patients without respiratory symptoms using spirometry (3,8,127). Even though pre-bronchodilator spirometry is relatively inexpensive, the economic and public health costs are considered too comprehensive for such a screening (8). However, active case finding may be relevant (3). A study by Moretz et al. (2015) developed and validated a predictive model aiming to identify patients with undiagnosed COPD. The optimal predictive model included 34 variables associated with a diagnosis of COPD. The model provided an acceptable level of accuracy (128). Such model shows an example of how characteristics associated with undiagnosed COPD may add to the identification of patients with undiagnosed COPD. A qualitative study by Leidy et al. (2015) identified 48 items that is to be tested quantitatively in a future study in combination with peak expiratory flow devises (129). In line herewith, Ronaldson et al. (2018) and Jihoo et al. (2013) suggest that COPD case finding may be improved by use of peak flow meters or microspirometers (130,131). Hence, it seems that development and optimization of COPD case-finding tools are in the pipeline.

Paper I does not explain why the subjects with a post-bronchodilator FEV1/FVC<0.7 were undiagnosed. Based on the results of Paper I, one may assume that mild representation of symptoms contributes to the underdiagnosis. However, it is not clear if the subjects remained undiagnosed because of an error in the diagnostic process or because the subjects had not seen a doctor. Mild representation of symptoms may cause a diagnostic delay until a more severe disease stage. The diagnostic delay may also be caused by lack of awareness and knowledge among healthcare professionals

(23). An example of this mild representation of symptoms is a study by Akamatsu et al. (2008). The authors found that 52% of their subjects did not have any respiratory symptoms despite having a COPD diagnosis (24). It must be presumed challenging to diagnose a patient with COPD if the patient does not complain about respiratory symptoms. Moreover, patients who are not bothered by respiratory symptoms may be less inclined to visit their general practitioner.

6.3.2 MISDIAGNOSIS OF COPD

As described in Paper II, there are several challenges linked to diagnosis of COPD. First, the patient in question needs to be identified, as described in Paper I. However, when a patient is identified and undergoes diagnostic evaluation, a multitude of diagnostic errors may occur in the process.

The challenges linked to the spirometry threshold are well recognized. It is essential for limiting misdiagnoses that consensus is reached regarding the proper diagnostic criteria (132). The fixed threshold of 0.70 seems to cause overdiagnosis of older patients and underdiagnosis of younger patients (27,28,52,53,55–57,60–66,68,72,78,79,81–83,133). However, Paper II did not find overall agreement that LLN should replace the fixed threshold of 0.7 (27,52,53,55,56,78,79,81,82). A shortcoming of the existing literature is the lack of a gold standard to which the threshold can be compared. Often, studies just compare LLN to 0.70 and vice versa. Hoesein et al. (2011) found that 9 of 18 studies used only LLN as reference test, which led to the conclusion that the choice between the fixed value and LLN could not be based on current literature (132). These findings are in agreement with the findings of Paper II. According to Hoesein et al. (2012), further longitudinal research is warranted in order to clarify the ideal threshold (132), but perhaps we should start seeking other options? Perhaps it is time to acknowledge that neither LLN nor 0.70 leads to a reliable COPD diagnosis. As demonstrated in Paper II, a great number of studies have questioned the threshold without reaching consensus.

The challenges of spirometry in COPD diagnosis and monitoring do not confine to the spirometry threshold alone. Spirometry may be insufficient for classification of lung abnormalities – independent of the threshold used (134). Brusasco et al. (2015) recommends that spirometry should not be used as the only pulmonary function test in COPD (134). Moreover, Doherty (2008) argues that spirometry alone is inadequate to monitor COPD (6). These statements are supported by study by Schermer et al. (2016), in which 14.3% of subjects shifted diagnostic category over time when spirometry was used for the diagnostic determination (135). These findings are in line with the results of Paper II, where it was found that errors linked to spirometry is a significant cause of misdiagnosis of COPD.

Spirometry also proves problematic for smokers. Woodruff et al. (2016) found that respiratory symptoms and exacerbations were common among current or former smokers with spirometry values within the normal range. On that basis, Woodruff et al. (2016) suggests that the current use of spirometry may not be adequate for diagnosis of smoking-related lung disease (136). These findings are similar to the findings of Regan et al. (2015) who found that lung impairment and disease were common among smoking subjects without COPD as defined by spirometry (137). These challenges may add to the severe underdiagnosis of COPD. Along these lines, the study presented in Paper II also identified smoking as a patient-related factor contributing to misdiagnosis of COPD.

Fourteen percent of the papers included in Paper II described misdiagnosis in cases of COPD with comorbidities (23,55,88,107–109,111–113). Comorbidities are common among patients with COPD (3) and aggravate the problem of misdiagnosis of patients with comorbidities. The challenge of differential diagnosis combined with the multifactorial challenges linked to spirometry may add to the fact that COPD misdiagnosis is also linked to the diagnostic practices of primary care. Primary care diagnosis is often discordant with a diagnosis made by a pulmonary specialist (84,86,87,90–92). Primary care should receive better diagnostic support than they do now (13, 57). Paper II found various setups designed for the support of primary care in the diagnosis of COPD (84,86,87,90–92). However, the ideal setup remains unclear.

6.3.3 ADJUSTMENT OF BRONCHODILATOR SPIROMETRY

Bronchodilator spirometry represents a challenge in COPD diagnosis as well. According to existing guidelines, COPD diagnosis should always be based on post-bronchodilator spirometry (3). However, post-bronchodilator spirometry is not always performed, and a diagnosis is then established based on pre-bronchodilator spirometry (30,32). Thus, bronchodilator spirometry represents a cause of misdiagnosis of COPD, as described in Paper II. Paper III accommodates this issue by suggesting an adjustment of threshold from 0.7 to 0.66 for pre-bronchodilator spirometry. However, even though such an adjustment may improve diagnostic accuracy, it does not solve the issue of misdiagnosis of COPD. The suggested adjustment may be considered a consolidation rather than a solution to the challenges of spirometry-based diagnosis of COPD.

The evidence regarding bronchodilator testing seems indecisive. A study by Mannino et al. (2011) found similar accuracy in pre- and post-bronchodilator spirometry for predicting mortality (138). Similarly, Hoesein et al. (2012) found no significant difference in diagnostic property between pre- or post-bronchodilator spirometry

(139). In contrast, Schermer et al. (2008) and Waheed et al. (2011) found that pre-bronchodilator spirometry cause overestimation of airflow obstruction (83,105). In line herewith, Probst-Hensch et al. (2010) found that pre-bronchodilator spirometry may cause misclassification of COPD (104). Chen et al. (2012) found pre-bronchodilator FEV1 to be inferior to post-bronchodilator FEV1 in the assessment of COPD severity (140). However, Fortis et al. (2017) found that post-bronchodilator spirometry may more accurately predict various COPD features and outcomes (141). Hence, the evidence for using bronchodilators seems less convincing. One may assume that part of the pre-bronchodilator misclassification is caused by the poor accuracy of the 0.7 threshold that was identified in Paper III.

In summary, it may be questioned whether spirometry leads to a reliable diagnosis of COPD. The multifaceted challenges linked to spirometry clearly calls for alternative pulmonary function tests for COPD diagnosis and monitoring.

6.3.4 PULMONARY FUNCTION TESTING ALTERNATIVES

In general, pulmonary function tests depend on patient effort. This dependence is obviously an issue, as patient effort is impossible to standardize (35). The SPOT test is expected to be independent of patient effort, which underlines its potential for telemonitoring as well as diagnosis of COPD. As mentioned previously, pulmonary function tests are seldom included in COPD telemonitoring trials (44). Their exclusion may, in part, be explained by the complexity of the existing pulmonary function tests. Patients cannot perform neither spirometry nor DLCO without verbal instruction during the tests (34). Thus, due to its simplicity, the SPOT test has potential application in telemonitoring.

Another challenge of existing pulmonary function tests is that it is very challenging to perform spirometry, body plethysmography, and DLCO with severe respiratory symptoms (34,119,142). Consequently, patients may be unable to perform pulmonary function tests during hospital admissions due to exacerbation. The SPOT test is not challenging to perform for patients in exacerbation and thus has potential application during hospital admission.

Obviously, the correlation between DLCO and the SPOT test is imperfect. The deviations may partly be explained by the variability of DLCO. The equipment-related variability of DLCO analyzers may comprise to 20% (143,144). Moreover, one should expect to see patient-related variability, equipment-related variability, and clinician-related variability. DLCO is also biased by smoking, and the existing DLCO guidelines do not compensate for carboxyhemoglobin sufficiently (38,145,146).

Smokers may have carboxyhemoglobin levels above 10%, whereas the carboxyhemoglobin level of healthy nonsmokers typically lies below 2%. When the carboxyhemoglobin level increases by 1%, it will cause a decrease of approximately 1% in DLCO (147). Carboxyhemoglobin may explain the variability of the smoking subjects included in Paper IV. The challenges related to DLCO obviously represents an issue when the SPOT test is assessed by using DLCO as a gold standard.

Paper IV found a poor correlation between FEV1 and the SPOT test and DLCO, respectively. These findings combined with the findings of Paper I-III underlines that COPD is highly challenging to diagnose. Patients with COPD may be affected more or less by emphysema or small airways disease (3) which complicate the diagnostic process. Although spirometry should not be used alone to diagnose and monitor COPD (133,134), it continues to be the key pulmonary function test in COPD. The SPOT test may serve as a potential supplement to spirometry in the diagnostic assessment. One may cautiously suggest that the SPOT test provides an estimate of level of emphysema, whereas spirometry may primarily provide an estimate of the level of chronic bronchitis. Such a combination would provide a more holistic approach when assessing lung function in COPD. We should not expect any pulmonary function test to stand alone in the diagnosis and monitoring of a disease as complex as COPD.

6.4 FUTURE PERSPECTIVES

COPD case finding can be optimized. As described, it seems that development and optimization of COPD case-finding tools are in the pipeline. This optimization may, among other things, focus on determining the role of specific characteristics of patients with undiagnosed COPD. The role of characteristics such as edema, peripheral artery disease, history of lower tract infection, educational level, age, income, occupation, and childhood illness is yet to be determined. Moreover, the role of flow meters in COPD case finding is also uncertain. Future studies may focus on algorithms based on characteristics of undiagnosed COPD in combination with flow meter testing in order to identify the optimal approach in COPD case finding.

To minimize cases of underdiagnosed or misdiagnosed COPD, the respiratory community needs to agree on the definition of COPD and on the threshold for defining COPD. One cannot expect primary care to determine a correct diagnosis on a fragile foundation. It is essential that future studies determine how to optimize the support of primary care in COPD diagnosis. Moreover, the evidence regarding bronchodilator spirometry seems unclear, and additional studies should explore the necessity of bronchodilator testing in COPD diagnosis. Further studies of the adjusted pre-

bronchodilator threshold of 0.66 suggested in Paper III would also add value, since post-bronchodilator spirometry is seldom performed in clinical practice.

As spirometry seems to be the main cause of misdiagnosis of COPD, future research should focus on alternative pulmonary function tests and biomarkers. Such research may focus on the SPOT test, but the potential of other pulmonary function tests and biomarkers should be explored as well. COPD is multifaceted, and we should not expect a single, isolated test to be able to determine diagnosis and disease progression.

Finally, future studies may determine the validity of the SPOT test as a future pulmonary function test for COPD. First, more subjects should undergo more or less the same procedure as that the 14 subjects who were included in Paper IV. Second, a study should aim to explore the potential of SPOT as a predictor of COPD exacerbation for potential implementation in telemedicine setups. This process would involve SPOT measurements in patients hospitalized for exacerbation compared to six weeks later when their condition has stabilized. Such studies should account for known biases such as carboxyhemoglobin. A study protocol for such a study has already been approved by the local ethical committee in the North Denmark Region.

CHAPTER 7: CONCLUSION

This chapter concludes the thesis.

In conclusion, the diagnosis of COPD proves challenging. Patients with COPD, who remain undiagnosed, are characterized by fewer respiratory symptoms and overall better health than their diagnosed counterparts. This challenge complicates the diagnostic process, as it may be difficult to identify patients with mild respiratory symptoms. Moreover, the diagnostic process is characterized by a multitude of causes of misdiagnosis. These causes of misdiagnosis are mainly linked to the key pulmonary function test in COPD – spirometry. Especially the threshold for defining COPD is heavily discussed as a cause of misdiagnosis of COPD.

COPD diagnosis may be improved by adjusting the pre-bronchodilator threshold of FEV1/FVC<0.7. An adjustment of the threshold to 0.66 may improve the diagnostic accuracy. However, the need for alternative pulmonary function tests in COPD is clear. The SPOT test is a novel pulmonary function test in COPD. The test correlated significantly with DLCO. Thus, the SPOT test seems promising as a future pulmonary function test for COPD. However, further validation of the SPOT test is needed. The role of the SPOT test in COPD diagnosis and monitoring is yet to be determined.

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